



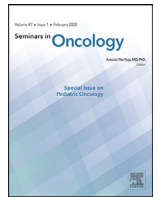
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# Are sex discordant outcomes in COVID-19 related to sex hormones?

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## ABSTRACT

COVID-19 has a clear sex disparity in clinical outcome. Globally, infection rates between men and women are similar; however, men are more likely to have more severe disease and are more likely to die. The causes for this disparity are currently under investigation and are most likely multifactorial. Sex hormones play an important role in the immune response with estrogen seen as immune boosting and testosterone as immunosuppressing. Additionally, an important protease involved in viral entry, TMPRSS2, is regulated by androgens. Many observational and prospective studies are ongoing or initiating to further examine the role of sex hormones in SARS-CoV-2 infection and if modulation of them is a realistic treatment option.

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## Introduction

Global epidemiological data have revealed sex discordant severity of disease and outcomes in patients with COVID-19 infections with males fairing FAR worse than females [1]. Many hypotheses have been put forward to explain this difference such as smoking, age, and co-morbid conditions [2,3]. These include differences in immune responses between the sexes. Estrogen and testosterone are both known to mediate immune responses, with testosterone an immune suppressor and estrogen an immune booster. A previous study has reported that SARS-CoV-2 entry into the host cell depends on the angiotensin converting enzyme (ACE) two receptor and cellular protease TMPRSS2. ACE2 is the cellular receptor that the SARS-CoV-2 spike protein binds to while TMPRSS2 is a serine protease that cleaves the S protein for viral priming [4]. TMPRSS2 expression is regulated in part by androgens and is a known biomarker of prostate cancer severity when fused with ERG [5,6]. This data brings questions to the forefront about the role sex hormones play in disease susceptibility and severity and whether their modulation could serve as a viable treatment option for SARS-CoV-2 infection. In addition, studies aimed at finding clinically relevant biomarkers to stratify outcome are important in resource limited settings, like those found in pandemic epicenters. Intense research efforts are currently underway to investigate the associa-

tion of sex hormones and ACE2/TMPRSS2 expression with COVID-19 severity as well as exploit inhibitors that target the sex steroid hormone pathway or modulate TMPRSS2 expression/activity as potential treatment options for the disease.

## Sex hormones are associated with immune response

Sex hormones play an important and dimorphic role in immune regulation and response. This difference is seen in both innate and adaptive immunity. Estrogen has been shown to enhance immunological markers and response [7]. Estrogen is also linked to T-cell proliferation [7]. In addition, X chromosome linked genes play a role in the heightened response of females. Females are known for a greater presence of autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus. Testosterone is seen as an immunosuppressive agent by down-regulating natural killer cells and tumor necrosis factor-alpha [7]. Often, over the course of an infection, females mount a more robust response. While this response can be effective in clearing the infection quicker, it can also contribute to immunopathological issues. Sex differences in immune response are directly attributed to the prevalence, severity, and outcomes of viral infections [8,9]. Notably, as with SARS-CoV-2, epidemiological data for MERS-CoV and SARS-CoV showed a similar trend toward worse outcomes in men [10,11] (Table 1).

## TMPRSS2 and ACE2 are co-expressed in tissues targeted by SARS-CoV-2

Co-expression of TMPRSS2 and ACE2 is found in the ciliated and secretory cells of the nasal cavity, providing important infor-

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**Table 1**  
Epidemiological data showing trends for worse outcomes in men with SARS-CoV, MERS-CoV and SARS-CoV-2

SARS [Case series 2003] [1]			
	Deceased (n = 1,139)	Survived (n = 385)	
Age, median (range) – yr	57 (45%–69%) <sup>A</sup>	32 (24%–44%)	
Male – n (%)	74 (53.2%) <sup>B</sup>	163 (42.3%)	
SARS cases [9]			
	Males v Females		
	RR <sup>C</sup>	95%CI	P value
0–44	2.27	1.25, 4.11	0.007
45–74	1.45	1.09, 1.93	0.014
≥ 75	1.02	0.81, 1.27	1.000
All	1.66	1.35, 2.05	<0.0001
MERS-CoV [8]			
	Cases	Deaths	Case fatality rate
Male n (%)	260 (62%)	89 (74%)	52%
Female n (%)	F 162 (38%)	31 (26%)	23%
COVID-19 [Public data set] [1]			
	Deceased (n = 37)	Survived (n = 1,019)	
Age, median (range) – yr	70 (65–81) <sup>D</sup>	47 (35–57)	
Male – n (%)	26 (70.3) <sup>E</sup>	510 (50)	

<sup>A</sup>  $P < 0.01$  v SARS survived patients.

<sup>B</sup>  $P < 0.05$  v SARS survived patients.

<sup>C</sup> RR, unadjusted relative risk.

<sup>D</sup>  $P < 0.01$  v COVID-19 survived patients.

<sup>E</sup>  $P < 0.05$  v COVID-19 survived patients.

**Table 2**  
Prostate cancer patients in Veneto region [31]

	Receiving ADT	Not receiving ADT	Odds ratio
Total number of patients	5,273	37,161	
Total number of patients testing positive for SARS-CoV-2	4	114	4.05 (1.55–10.59) $P = 0.0059$
Mild SARS-CoV-2 disease	3	83	3.93 (1.31–11.77) $P = 0.0199$
Severe SARS-CoV-2 disease	1	31	4.40 (0.76–25.50)

mation on means of transmissibility. Expression is also observed in the ciliated and secretory cells of the lungs [12,13]. Clinical reports note that infection of type-2 pneumocytes in the lower respiratory track is important in the development of severe lung symptoms [14]. However, co-expression also occurs in many tissues outside the lungs, providing alternative sites for viral infection (Fig. 1). These areas include the eyes, esophagus, heart, ileum, colon, gallbladder, brain, testes, and prostate [12,15]. It is known that TMPRSS2 expression is upregulated by androgens in prostate cancer cell lines and *in vivo* [16,17]. Important questions remain to be answered regarding the effect of androgens on the expression of both ACE2 and TMPRSS2 in the lungs and other tissues vulnerable to viral infection. In a preprint study, researchers concluded that TMPRSS2 expression in lungs was not mediated by androgens or by enzalutamide, an agent that decreases androgen receptor signaling [18]. It may be that the cell types must be separated to see the effect as there is co-expression in club cells of the prostate and lungs [19]. Additionally, are other hormones involved in modulation of TMPRSS2 expression? Estrogen is known to regulate the TMPRSS2-ERG fusion in prostate cancer [20], however, its role outside of prostate cancer and this fusion is unknown. Studies are also ongoing to evaluate the association of genetic polymorphisms

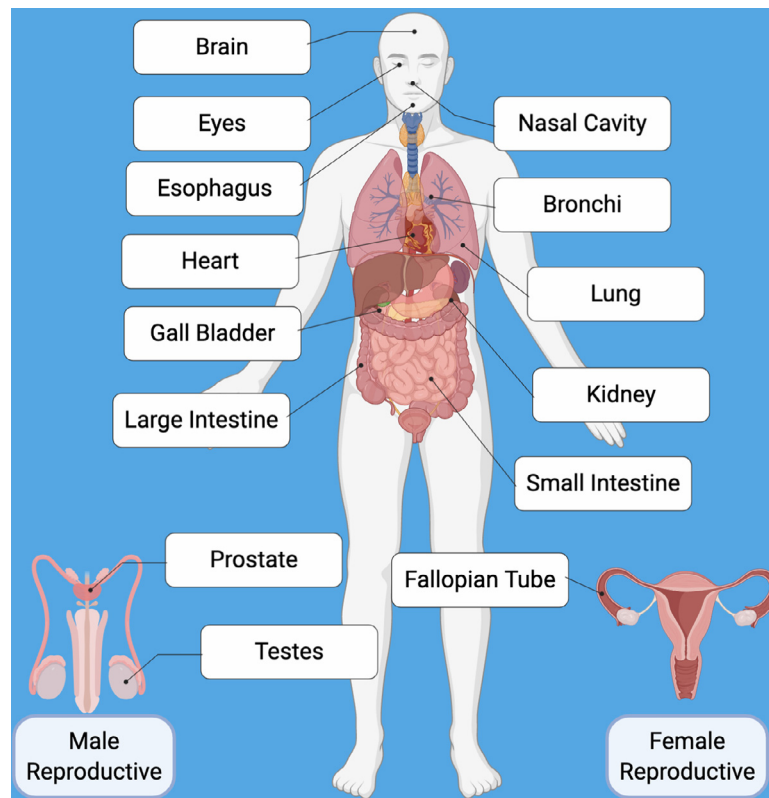
and/or mutations that cause disparate expression of TMPRSS2 and ACE2 with COVID-19-related outcomes. A recent development is that TMPRSS2 may be circulating and able to act on cells without membrane expression [21]. It has been reported that prostate cancer cell lines *in vitro* and *in vivo* shed the protease [22]. Whether soluble TMPRSS2 is involved in mediating viral infection is an interesting concept that warrants further study [23].

### Patient populations to observe for outcomes

If sex hormones play an important role in the disparity of COVID-19 outcomes, then correlative studies can be conducted across various patient populations to investigate for associations with abnormal hormone levels or genetics. In men and women, hypogonadism, or the inability to properly produce sex hormones, can be split into two types, hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism. The former is characterized by dysfunction at the primary gonads whereas the latter results from a dysfunction of the pituitary or hypothalamus. Some examples are Prader-Willi syndrome, Turner syndrome, and Klinefelters syndrome [24]. The specific abnormality, low testosterone or low estrogen, will determine the hypothesized outcome in relation to COVID-19. Additionally, men undergoing androgen deprivation therapy (ADT) and women on hormone therapy for various forms of cancer may have lower hormone levels than normal. On the other side, patient populations with increased levels of sex hormones can also be observed. In men, these include individuals taking testosterone replacement therapy and men with a genetic predisposition to higher testosterone or androgen receptor signaling (androgenic alopecia [AGA], benign prostatic hyperplasia[25]). Females with polycystic ovary syndrome have increased androgen levels and have been proposed as a sub-group to observe [26]. If sex hormones play an important role, these patient populations represent groups that may have outcomes different from matched individuals of the same sex. It is not known at which stage of infection these hormones may affect outcomes. Notably, two preprint studies have analyzed sex hormone levels in men presenting to or in hospital care for COVID-19. They found that testosterone levels are decreased and gonadal function is altered [27,28]. It is possible that as the disease progresses, the viral infection begins to affect testosterone levels. Knowing the timing of this event is important in understanding where in the course of infection androgen levels determine outcome. In a recent preprint study, analysis of clinical data on patients with COVID-19 from the UK Biobank and Yale New Haven Hospital identified an association between androgen imbalance and disease complications in male patients [29].

### Observation of AGA to correlate to high androgen and outcome

AGA is a clinical condition that affects men and is regulated by androgens and androgen receptor expression. AGA is considered the most common cause of male pattern hair loss. The idea to look for AGA in men suffering with COVID-19 was first proposed by Goren et al [26]. They hypothesized that men diagnosed with AGA would represent a population with higher androgen and androgen signaling. In a study of preliminary observations in Spain, 71% (29 of 41) of men diagnosed with COVID-19 related bilateral pneumonia were also diagnosed with AGA [30]. In a follow-up report, the researchers have expanded their patient population to 175 hospital admitted COVID-19 positive men and women. During the course of the study, men accounted for a majority of those admitted (122 of 175) and 79% of them had observed AGA using the Hamilton-Norwood scale for men and the Ludwig scale for females [31]. What these studies are missing, and what future studies could benefit from are robust clinical laboratory values for sex hormones over the course of the disease.



**Fig. 1.** Indicated locations of expression for co-expression ACE2 and TMPRSS2. These locations may provide insight into SARS-CoV-2 infection profile and clinical manifestations. Figure produced using Biorender.com.

### ADT and SARS-CoV-2 infection

Hormone therapy for prostate cancer, also called ADT, refers to treatments that block the production or use of androgens. ADT is the mainstay of treatment for prostate cancer and is used to reduce testosterone production in the testicles to prevent androgen-mediated tumor growth. ADT includes agonists and antagonists of upstream hormones that control androgen release such as LHRH agonists (leuprolide, goserelin, triptorelin, and histrelin) and LHRH antagonists (degarelix). ADT is often continued until disease progression or death. First-generation antiandrogens (flutamide, bicalutamide, and nilutamide) are receptor antagonists that target AR translocation and subsequent AR signaling. Second-generation antiandrogens inhibit pathways involved in persistent androgen production or AR signaling from residual androgens produced in extragonadal sources and include biosynthesis inhibitors (abiraterone, a CYP17 inhibitor) and next generation AR antagonists (enzalutamide, apalutamide, and darolutamide) [32]. ADT has been shown to decrease the risk of autoimmune disorders and has been proposed as a treatment option in these disorders [33]. A recent study by Montopoli et al proposed a link between ADT and reduced COVID-19 risk [34] (Table 2). The authors analyzed data from the heavily studied Veneto region of Italy and included data from 4,532 men who tested positive for SARS-CoV-2. Of these patients, 430 (9.5%) had cancer and 118 (2.6%) had prostate cancer (28% of all cancers). Consistent with other publications, men with cancer have worse disease presentations than men without cancer, even when stratified for age. In the region, 5,273 prostate cancer patients are on ADT; however, only four of these patients were positive for SARS-CoV-2. Even with small numbers, the authors conclude that men positive for SARS-CoV-2 and on ADT not

only had improved outcomes over other men with prostate cancer patients positive for SARS-CoV-2, but that ADT may have reduced the chance of infection. They concluded that ADT had a protective effect in men positive for SARS-CoV-2 infection. While there are many limitations to this study including small sample size and not reporting ADT therapy used, it provides the first evidence that reducing androgens or their effect on tissues may have a beneficial impact on outcomes in men infected with SARS-CoV-2. Following Montopoli et al, additional studies into androgen modulation are necessary. Specifically, a large collaboration pooling data from across institutions is required to confirm the study findings of Montopoli et al and determine whether androgen-deprivation treatment may be an effective approach for men with COVID-19.

### Current clinical trials that address sex hormone treatment or TMPRSS2 and COVID-19

Clinical trials have been initiated worldwide aimed at targeting sex hormone pathways or TMPRSS2 directly and these are summarized in Table 3. Each trial has different primary and secondary endpoints relative to the drug they are using and rationale. At the time of writing, there are nine studies in various stages that utilize direct or indirect inhibitors of TMPRSS2. Two direct TMPRSS2 inhibitors are camostat and nafamostat, both of which are approved in Japan for pancreatitis [4,35]. The third is an expectorant called bromhexine [17]. The rationale for the nine clinical trials testing these direct TMPRSS2 inhibitors is that inhibition of the protease activity of TMPRSS2 will prevent viral entry. Some of these studies are in combination with hydroxychloroquine that has been shown to be effective *in vitro* against SARS-CoV-2 [36].

**Table 3**  
COVID clinical trials for direct and indirect TMPRSS2 inhibitors

Drug class	Drug name	Target	Effect	ClinicalTrials.gov identifier	Primary outcome	Sponsor/Location
LHRH antagonist	Degarelix	GnRH	<ul style="list-style-type: none"> <li>Decreases androgens</li> </ul>	NCT04397718	<ul style="list-style-type: none"> <li>Reduction in composite endpoint of mortality, ongoing need for hospitalization, or requirement for ECMO at Day 15 after randomization</li> </ul>	Veterans Administration Hospital locations in Los Angeles, Brooklyn, Manhattan, Seattle, USA
ER agonist	Estrogen	Estrogen Receptor	<ul style="list-style-type: none"> <li>Estrogen effects</li> <li>Decreases androgen</li> </ul>	NCT04359329	<ul style="list-style-type: none"> <li>Rate of hospitalization admission (30 d)</li> <li>Rate of transfer to ICU (30 d)</li> <li>Rate of intubation (30 d)</li> <li>Rate of death (30 d)</li> <li>Proportion of lung injury score decreased or increased after treatment</li> </ul>	Stony Brook University Hospital, NY, USA
Selective ER modulator	Tamoxifen	Estrogen Receptor	<ul style="list-style-type: none"> <li>Decreases estrogen production</li> <li>Increases testosterone production</li> </ul>	NCT04389580 in combination with isotretinoin		Kafrelsheikh University Egypt
Progestogen hormone	Progesterone	Progesterone Receptor	<ul style="list-style-type: none"> <li>Decreases androgen</li> <li>Decreases estrogen effects</li> </ul>	NCT04365127	<ul style="list-style-type: none"> <li>Change in clinical status at day 15</li> </ul>	Cedars Sinai Medical Center, CA, USA
TMPRSS2 inhibitor	Camostat	TMPRSS2	<ul style="list-style-type: none"> <li>Decreases TMPRSS2 action</li> </ul>	NCT04353284	<ul style="list-style-type: none"> <li>Change in SARS-CoV-2 viral load</li> <li>Not hospitalized (14 d from baseline)</li> </ul>	Yale University, CT, USA
				NCT04338906 in combination with hydroxychloroquine		Heinrich-Heine University, Germany
				NCT04374019		University of Kentucky, KY, USA
				NCT04321096		University of Aarhus, Denmark
	Nafamostat	TMPRSS2	<ul style="list-style-type: none"> <li>Decreases TMPRSS2 action</li> </ul>	NCT04355052 in combination with hydroxychloroquine	<ul style="list-style-type: none"> <li>Clinical deterioration (14 d)</li> <li>Days to clinical improvement from enrollment</li> <li>Clinical state by NEWS scoring, positive PCR</li> </ul>	Sheba Medical Center, Israel
Bromhexine	TMPRSS2	<ul style="list-style-type: none"> <li>Decreases TMPRSS2 action</li> </ul>	NCT04352400	<ul style="list-style-type: none"> <li>Time-to-clinical improvement (day 1–28)</li> </ul>	University Hospital Padova, Italy	
				NCT04355026	<ul style="list-style-type: none"> <li>Duration of hospitalization through study completion</li> <li>Duration of disease through study completion</li> </ul>	General and Teaching Hospital Celje, Slovenia
				NCT04273763 in combination with hydroxychloroquine	<ul style="list-style-type: none"> <li>Time to clinical recovery after treatment (within 14 days of treatment start)</li> <li>Rate of aggravation (within 14 d of treatment start)</li> </ul>	Wenzhou Medical University, China
				NCT04340349 in combination with hydroxychloroquine	<ul style="list-style-type: none"> <li>PCR negative at day 0, 30, 60</li> <li>Serological negative at day 0</li> </ul>	Instituto Nacional de Rehabilitacion, Mexico
Antiandrogen	Bicalutamide	Androgen receptor	<ul style="list-style-type: none"> <li>Decreases androgens</li> </ul>	NCT04374279	<ul style="list-style-type: none"> <li>Number of participants with clinical improvement at day 7 after randomization</li> </ul>	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, MD, USA
Aldosterone antagonist	Spirolactone	Androgen receptor	<ul style="list-style-type: none"> <li>Decreases androgen signaling</li> </ul>	NCT04345887	<ul style="list-style-type: none"> <li>5-day improvement in oxygenation (p/f ratio)</li> </ul>	Istanbul University, Turkey



Indirect modulators of TMPRSS2 attempt to block the sex steroid hormone pathway. A trial is investigating the protective and immunomodulatory effects of estrogen in reducing the severity of COVID-19 outcomes in both male and female patients (NCT04359329). Similar in concept to the estrogen study is a trial assessing the safety and efficacy of progesterone for the treatment of COVID-19 in hospitalized men to examine the drug's anti-inflammatory properties to dampen the cytokine storm observed in SARS-CoV-2 infection. Somewhat contrary to the studies and rationale discussed is a study that is investigating tamoxifen in combination with isotretinoin as a treatment (NCT04389580). The study rationale is that isotretinoin decreases ACE2 expression and tamoxifen is involved in vesical transport, cellular pH, prevention of lung fibrosis, and reduction of serum TGF $\beta$ -1 levels. Not mentioned is the potential effects of tamoxifen on testosterone and estrogen [37,38]. In men treated with tamoxifen, an increase in testosterone was observed clinically [37]. Recently added to Clinicaltrials.gov is a study titled HITCH (NCT04397718), detailed in a press release from the Veterans Administration [39]. HITCH will enroll hospitalized Veterans to be given degarelix, a LHRH antagonist. Degarelix will be used to suppress testosterone production and potentially reduce viral burden by decreasing TMPRSS2 expression. A phase 2, randomized, open-label study at Johns Hopkins will be evaluating bicalutamide v standard of care in patients with COVID-19 requiring inpatient hospitalization (NCT04374279) to determine if bicalutamide improves the time to clinical improvement. Bicalutamide can not only suppress androgen activity but also raise estrogen levels which has been shown to have protective effects against acute lung injury [40]. Lastly, there is a study to evaluate the effects of spironolactone on oxygenation in COVID-19 patients with acute respiratory distress syndrome (NCT04345887). Spironolactone is a steroid that blocks the hormone aldosterone and has been known to have moderate antiandrogenic properties with some estrogen-like effects [41].

It is expected that many more trials will be launched as observations and results are reported. At the time of writing, we are aware of two additional studies being planned in Europe to evaluate enzalutamide in patients with COVID-19; these trials are not yet registered with Clinicaltrials.gov. In silico drug screening efforts have identified the androgen-AR signaling axis, specifically 5-alpha reductase inhibitors (dutasteride and finasteride), involved in modulating both ACE2 and TMPRSS2 levels, making these compounds potential drug candidates for further investigation [29]. In recent study, abiraterone was shown to inhibit in vitro SARS-CoV-2 activity, demonstrating another potential treatment for COVID-19 [42]. The scientific community is racing against time in search of a cure for COVID-19 and collaborative efforts are called upon to gather as much data and samples as possible to elucidate the sex disparity observed in disease outcomes [43]. A recent study of abiraterone demonstrated the ability to decrease viral load by about 70%. This data may be used to initiate a study of abiraterone in the near future [42].

## Conclusion

As the pandemic continues, important questions must be answered to elucidate the reasons some individuals are affected more severely than others. This data has many implications. First, as governments begin to reopen after lockdowns, a major strategic point is to continue to sequester the populations that are most vulnerable. Next, knowledge of who may progress to severe disease can help health care officials know where to mobilize resources. As seen in many of the most-affected communities, limited resources in overrun hospitals lead to worse outcomes. Finally, underlying differences in outcome may inform researchers on potential therapeutic targets. Manipulation of genes and pathways important to

viral replication and spread are hallmarks of antiviral treatment. We don't yet know if SARS-CoV-2 will reemerge or become a seasonal threat. The more information we gather now the better prepared we will be to deal with similar infections in the future.

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## References

- [1] Jin JM, Bai P, He W, et al. Gender differences in patients with COVID-19: focus on severity and mortality. *Front Public Health* 2020;8:152.
- [2] Sharma G, Volgman AS, Michos ED. Sex differences in mortality from COVID-19 pandemic: are men vulnerable and women protected? *JACC Case Rep* 2020.
- [3] Cai H. Sex difference and smoking predisposition in patients with COVID-19. *Lancet Respir Med* 2020;8:e20.
- [4] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–80 e8.
- [5] Hagglof C, Hammarsten P, Stromvall K, et al. TMPRSS2-ERG expression predicts prostate cancer survival and associates with stromal biomarkers. *PLoS One* 2014;9:e86824.
- [6] Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science* 2005;310:644–8.
- [7] Taneja V. Sex hormones determine immune response. *Front Immunol* 2018;9:1931.
- [8] Klein SL. Sex influences immune responses to viruses, and efficacy of prophylaxis and treatments for viral diseases. *Bioessays* 2012;34:1050–9.
- [9] Ghosh S, Klein RS. Sex drives dimorphic immune responses to viral infections. *J Immunol* 2017;198:1782–90.
- [10] Alghamdi IG, Hussain II, Almalki SS, Alghamdi MS, Alghamdi MM, El-Sheemy MA. The pattern of Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive epidemiological analysis of data from the Saudi Ministry of Health. *Int J Gen Med* 2014;7:417–23.
- [11] Karlberg J, Chong DS, Lai WY. Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? *Am J Epidemiol* 2004;159:229–31.
- [12] Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nature Medicine* 2020;26:681–7.
- [13] Lukassen S, Chua RL, Trefzer T, et al. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. *EMBO J* 2020:e105114.
- [14] Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J* 2020:55.
- [15] Qi J, Zhou Y, Hua J, et al. The scRNA-seq expression profiling of the receptor ACE2 and the cellular protease TMPRSS2 reveals human organs susceptible to COVID-19 infection. *bioRxiv* 2020:2020.04.16.045690.
- [16] Fernandez EV, Reece KM, Ley AM, et al. Dual targeting of the androgen receptor and hypoxia-inducible factor 1alpha pathways synergistically inhibits castration-resistant prostate cancer cells. *Mol Pharmacol* 2015;87:1006–12.
- [17] Lucas JM, Heinlein C, Kim T, et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. *Cancer Discov* 2014;4:1310–25.
- [18] Baratchian M, McManus J, Berk M, et al. No evidence that androgen regulation of pulmonary TMPRSS2 explains sex-discordant COVID-19 outcomes. *bioRxiv* 2020.04.21.051201.
- [19] Song H, Seddighzadeh B, Cooperberg MR, Huang FW. Expression of ACE2, the SARS-CoV-2 receptor, and TMPRSS2 in prostate epithelial cells. *Eur Urol* 2020.
- [20] Setlur SR, Mertz KD, Hoshida Y, et al. Estrogen-dependent signaling in a molecularly distinct subclass of aggressive prostate cancer. *J Natl Cancer Inst* 2008;100:815–25.
- [21] Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* 2020;181(5):1016–1035.e19.
- [22] Afar DE, Vivanco I, Hubert RS, et al. Catalytic cleavage of the androgen-regulated TMPRSS2 protease results in its secretion by prostate and prostate cancer epithelia. *Cancer Res* 2001;61:1686–92.
- [23] Strobe JD, Pharm DC, Figg WD. TMPRSS2: potential biomarker for COVID-19 outcomes. *J Clin Pharmacol* 2020;60(7):801–7.
- [24] Viswanathan V, Eugster EA. Etiology and treatment of hypogonadism in adolescents. *Pediatr Clin North Am* 2011;58:1181–200 x.
- [25] Izumi K, Mizokami A, Lin WJ, Lai KP, Chang C. Androgen receptor roles in the development of benign prostate hyperplasia. *Am J Pathol* 2013;182:1942–9.

- [26] Goren A, McCoy J, Wambier CG, et al. What does androgenetic alopecia have to do with COVID-19? An insight into a potential new therapy. *Dermatol Ther* 2020:e13365.
- [27] Schroeder M, Tuku B, Jarczak D, et al. The majority of male patients with COVID-19 present low testosterone levels on admission to Intensive Care in Hamburg, Germany: a retrospective cohort study. *medRxiv* 2020:20073817 2020.05.07.
- [28] Ma L, Xie W, Li D, et al. Effect of SARS-CoV-2 infection upon male gonadal function: a single center-based study. *medRxiv* 2020:20037267 2020.03.21.
- [29] Ghazizadeh Z, Majd H, Richter M, et al. Androgen regulates SARS-CoV-2 receptor levels and is associated with severe COVID-19 Symptoms in men. *bioRxiv* 2020:091082 2020.05.12.
- [30] Goren A, Vano-Galvan S, Wambier CG, et al. A preliminary observation: male pattern hair loss among hospitalized COVID-19 patients in Spain - a potential clue to the role of androgens in COVID-19 severity. *J Cosmet Dermatol* 2020.
- [31] Wambier CG, Vano-Galvan S, McCoy J, et al. Androgenetic alopecia present in the majority of hospitalized COVID-19 patients - the "Gabrin sign". *J Am Acad Dermatol* 2020.
- [32] Gamat M, McNeel DG. Androgen deprivation and immunotherapy for the treatment of prostate cancer. *Endocr Relat Cancer* 2017;24:T297–310.
- [33] Liu JM, Yu CP, Chuang HC, Wu CT, Hsu RJ. Androgen deprivation therapy for prostate cancer and the risk of autoimmune diseases. *Prostate Cancer Prostatic Dis* 2019;22:475–82.
- [34] Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (n=4532). *Ann Oncol* 2020.
- [35] Hoffmann M, Schroeder S, Kleine-Weber H, Muller MA, Drosten C, Pohlmann S. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. *Antimicrob Agents Chemother* 2020:64.
- [36] Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020;6:16.
- [37] Rambhatla A, Mills JN, Rajfer J. The role of estrogen modulators in male hypogonadism and infertility. *Rev Urol* 2016;18:66–72.
- [38] Lum SS, Woltering EA, Fletcher WS, Pommier RF. Changes in serum estrogen levels in women during tamoxifen therapy. *Am J Surg* 1997;173:399–402.
- [39] Richman M. VA scientists race to determine effectiveness of prostate cancer drug in treating COVID-19 patients. *VA Res Currents* 2020.
- [40] Hamidi SA, Dickman KG, Berisha H, Said SI. 17beta-estradiol protects the lung against acute injury: possible mediation by vasoactive intestinal polypeptide. *Endocrinology* 2011;152:4729–37.
- [41] Corvol P, Michaud A, Menard J, Freifeld M, Mahoudeau J. Antiandrogenic effect of spiro lactones: mechanism of action. *Endocrinology* 1975;97:52–8.
- [42] Yuan S, Chan JFW, Chik KKH, et al. Discovery of the FDA-approved drugs bexarotene, cetilistat, diiodohydroxyquinoline, and abiraterone as potential COVID-19 treatments with a robust two-tier screening system. *Pharmacol Res* 2020:104960.
- [43] Salonia A, Corona G, Giwercman A, et al. SARS-CoV-2, testosterone and frailty in males (PROTEGGIMI): a multidimensional research project. *Andrology* 2020.